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LETTERS TO THE EDITOR

Paul G. McDonough, M.D.
Associate Editor

Long-term response to naltrexone in polycystic ovary syndrome?

To the Editor:

In a recent article Fruzzetti et al. (1) have reported that in women with polycystic ovary syndrome (PCOS), the 6-month administration of the opioid-antagonist naltrexone at the dose of 50 mg/day improves menstrual cyclicity, reduces ovarian hyperandrogenism, and decreases the LH response to GnRH. They question whether an elevation of opioids may be directly involved in the increased LH secretion of women with PCOS, as a reduction of the inhibitory hypothalamic control of opioid peptides on gonadotropins has been proposed as one of the pathogenetic mechanism of the syndrome (1). To understand this point, it should be clear that the levels of peripheral opioids, which are synthesized by the pituitary and peripheral organs, do not reflect activity of hypothalamic opioids, which are within the blood-brain barrier. Hypothalamic opioids inhibit GnRH, whereas peripheral opioids may exert different effects including that of increasing the LH response to GnRH. A specific study performed by our group in estrogenized postmenopausal women strongly supports this possibility (2). Whether the same is true in women with PCOS, who have elevated levels of opioids and an enhanced LH response to GnRH, was also tested in a double-blind placebo controlled study (3). The results showed that a 5-day naltrexone administration (50 mg/day) does not reduce the LH response to a submaximal dose of GnRH (10μg i.v. bolus). Five days is the length of time sufficient to induce a complete block of opioid receptors at the pituitary, but insufficient to induce weight modifications, as those reported by Fruzzetti et al., after 6 months of treatment (1). Accordingly, weight reduction and the related endocrine modifications, rather than a direct effect at the pituitary, are a more likely mechanism to explain the clinical and endocrine response to naltrexone. Although the glucose-to-insulin ratio used by Fruzzetti et al. (1) is not sufficiently accurate to evaluate insulin resistance and its modifications (4), the documented decline of insulin levels is of relevance, but, as they mention, this has been already reported in previous studies with naltrexone. Experimental data suggest that elevation of insulin and insulin-like growth factor I (IGF-I) can be associated with an increased pituitary response to GnRH (5). Consequently, the cascade of positive events related to a reduction in insulin levels may include a decrease in the LH response to GnRH. The effect of naltrexone was not compared to placebo or weight reduction regimens. Controlled studies are required to evaluate the clinical efficacy of naltrexone in PCOS.

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Reply of the Authors:

We thank Drs. Cagnacci and Paoletti for their interest in our article. We agree with their hypothesis that the beneficial effects on menstrual cyclicity and endocrine profile obtained in obese women with polycystic ovary syndrome (PCOS) treated with naltrexone may be the consequences of weight loss and related endocrine modifications rather than to a direct effect of the drug on opioidergic tone at the pituitary level. However, study design limitations (sample size) and the lack of a control group did not allow us to firmly sustain this conclusion.

As discussed in the article, we used fasting glucose-to-insulin ratio to assess insulin sensitivity. The usefulness of this screening has been tested in obese, non-Hispanic white women, by Legro et al. (1). The published data of this study indicate that a fasting glucose-to-insulin ratio is a good

measure of insulin sensitivity, that is, it has both high sensitivity and specificity for detecting insulin-resistant women. We know that other more complex tests may be used, but at present, there are no other studies that have refuted the validity of this ratio. The strength and convenience of this ratio for evaluating insulin sensitivity will require continued evaluation.

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Comparative efficacy of hydroxyethyl starch and Haemaccel in the treatment of severe ovarian hyperstimulation syndrome

To the Editor:

With interest we have read the paper of Gamzu and co-workers (1). However, we are profoundly surprised about some of the results.

Haemaccel (Aventis Pharma, Frankfurt, Germany) is a volume replacement solution with 3.5% urea-linked gelatin. From the actual scientific knowledge its volume effect has been proven to be shorter and of less extent than the volume effect of HAES-steril 10% (Fresenius Kabi, Bad Homburg, Germany), a volume substitute consisting of 10% HES 200/0.5 (2–4). Some data even show a marked difference between the volume effects of these two solutions (5).

Thus, we cannot understand why Gamzu and co-workers found patients in the hydroxyethyl starch (HES) group needing about one-third more volume (mean, 3,808 mL HES solution) than patients in the gelatin group (mean, 2,667 mL gelatin solution). In addition, we are surprised about the fact that these different dosage regimens lead to a comparable reduction in hematocrit (mean, 7% in each group). The only slightly elevated urine excretion in the HES group (mean, 1,336 mL/24 hour compared with mean of 1,217 mL/24 hour in the gelatin group) cannot explain these findings.

The different demand in colloidal solutions could be caused by differences in severity of ovarian hyperstimulation syndrome being more pronounced in the HES group. However, this also cannot explain the hematocrit findings. We suppose that there must have been additional factors involved that are not obvious from the article. If such additional factors existed, the conclusions from the results have to be reconsidered.

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Reply of the Author:

We kindly welcome the interest of Schimetta and co-workers in our recent article. From the physicochemical point of view, hydroxyethyl starch (HES) with MW of 200 kD and 0.5 degree of substitution are regarded as rapidly degradable. Such molecules are relatively quickly split in vivo into smaller, more favorable molecule sizes, resulting in faster renal elimination, shorter volume effect, and fewer adverse effects on coagulation and rheological parameters. Although, these medium mass HES still may have longer fluid effect than 3.5% urea-linked gelatin (Haemaccel) (1), this difference is modest compared to HES's with high MW, high degree of substitution or high C2/C6 ratio. Accordingly, such physicochemical differences may not translate to clinical end points such as hematocrit (2) in other medical situations, as well as in ovarian hyperstimulation syndrome (OHSS) (3).

Although the differences in the total volume used in the HES compared with the gelatin group (mean, 3,808 mL HES vs. a mean of 2,667 mL gelatin solution) did not reach statistical significance, we agree it is puzzling. We speculate it may result from issues of learning curve and clinical confidence in the use of a new product (HES).